

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 8

#### REMARKS

The specification has been amended to make a reference to the Sequence Listing, attached hereto. Applicants submit that the amendment of the specification raises no issues of new matter and is fully supported by the specification as filed. Applicants respectfully request that this Amendment be entered.

Claims 1-15 were pending in the subject application. Applicants have hereinabove amended claims 1, 2, 4, 7-12 and 15 and have canceled claims 6, 13 and 14. Claim 1 was amended to recite that the linker peptide is cleavable and is recognized by blood coagulation factor. Claims 2 and 4 were amended to clarify the group of proteins from which a portion of the fusion protein was selected and claim 2 was further amended to clarify that the selected protein activate thrombolytic factors. Claims 7-11 were amended to fix claim dependencies and/or to recite the SEQ ID NO to which the listed sequences refer. Claim 10 was also amended so that it is now in independent form and includes all of the limitations of the base claim and any intervening claims. Claim 11 was also amended to correct typographical errors and to state that the fusion peptide is cleavable. Claims 12 and 15 were amended to state that the claimed fusion protein is the fusion protein of claim 1. Support for these amendments may be found, *inter alia*, in original claims 1 and 6 and in the specification at paragraphs [0009], [0019] and [0020] and in amended paragraphs [0021] and [0024]. Applicants maintain that no issue of new matter is raised by this amendment. Upon entry of the Amendment, claims 1, 2, 4, 7-11, 12 and 15, as amended, and claims 3 and 5 will be pending and under examination.

#### Informalities

The Examiner objected to the disclosure, stating that the specification recites amino acid sequences such as IEGR, GSIEGR, PRIEGR, GSGPR and GSLGPR at pages 3, 4 and 7-8 without providing sequence identifiers "SEQ ID NO:". The Examiner also stated that the application allegedly fails to comply with the requirements of 37 C.F.R. §1.821-1.825. In response, applicants submit herewith as **Exhibit A** a paper copy of the

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 9

Sequence Listing, a C.R.F. Sequence Listing as **Exhibit B**, and a Statement in Accordance with 37 C.F.R. §1.821(f) as **Exhibit C and have amended the specification to include the sequence identifiers as requested by the Examiner.** Applicants maintain that the Sequence Listing attached hereto contains no new matter. Applicants therefore respectfully request that the Examiner reconsider and withdraw this objection to the disclosure.

#### **Objection to New Matter Added to Specification**

The Examiner objected to the supplemental amendment filed April 3, 2009 because the April 3, 2009 amendment allegedly introduces new matter into the disclosure of the invention which is not supported by the original disclosure. Specifically, the Examiner stated that the added material which is not supported by the original disclosure is as follows: a linker peptide recognized by a blood coagulation factor refers to a tetrapeptide of LGPR (originally cited as tripeptide of GPR) or peptide containing LGPR or LGPL (originally cited as GPR) (paragraphs [0011], [0021], [0024]).

In response, applicants respectfully traverse the Examiner's rejection. Applicants maintain that the amendment of "GPR" to "LGPR" merely relates to an obvious error, and does not introduce new matter, at least for the following reasons. First, the examples in the present application only relate to the technical solution, which utilize the linker peptide "GSLGPR", but not "GSGPR". In example 3, the fusion protein STH (staphylokinase linked to hirudin via the sequence "GSLGPR" recognized by thrombin) is prepared. Accordingly, from example 3, one of ordinary skill in the art will recognize that "GSGPR" is obviously wrong. Furthermore, the inventors determined the nucleotide sequence for the fusion protein STH. A copy of the sequencing results, which shows that the nucleotide sequence for the linker peptide between staphylokinase and hirudin is "GGA TCC CTG GGT CCG CGT", which corresponds to the amino acid sequence "GSLGPR", is attached hereto as **Exhibit D**, wherein the nucleotide sequence corresponding to the linker peptide is underlined.

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 10

Additionally, it is known in the art that the peptide bond recognized and cleaved by thrombin is the one formed by the carboxyl group of lysine or arginine and the amino group of the downstream amino acid. Accordingly, the recognition sequences for thrombin are not unique, and many short peptides comprising lysine or arginine may be recognized and cleaved by thrombin. See, e.g., Richard J. Jenny et al., *Protein Expression and Purification*, 2003, 31: 1-11 at page 2, right hand column paragraph 3, Table 1 and Table 2; see also, U.S. Patent No. 5,298,599, column 6, lines 27-33, which shows that the linker peptide "GSLGPR" may be recognized and cleaved by thrombin. Copies of Jenny et al. and U.S. Patent No. 5,298,599 are attached hereto as **Exhibit E** and **Exhibit F**, respectively. Applicants therefore respectfully request that the Examiner reconsider and withdraw this objection to the disclosure.

#### **Claim Objections**

The Examiner objected to claims 7-11 because the claims recite amino acid sequences without providing a sequence identifier "SEQ ID NO:".

In response, applicants have hereinabove amended claims 7-11 to recite, in relevant part, the proper SEQ ID NO. Applicants therefore respectfully request that the Examiner reconsider and withdraw this objection to the disclosure.

#### **Rejection under 35 U.S.C. §101**

The Examiner rejected claims 13-14 under 35 U.S.C. §101 because the claimed recitation of use allegedly results in an improper definition of a process, i.e. results in a claim which is not a proper process claim under 35 U.S.C. 101.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution and without conceding the correctness of the Examiner's position, applicants have hereinabove canceled claims 13 and 14. Applicants therefore respectfully request that the Examiner reconsider and withdraw this rejection.

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 11

**Rejection under 35 U.S.C. §112, First Paragraph**

The Examiner rejected claims 8, 9 and 11 under 35 U.S.C. §112, First Paragraph, as failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner stated that this was a new matter rejection. The Examiner stated that although Example 3 indicates preparation of fusion protein of STH (SAK-GSLGPR-HV2), and even though is known in the art that the thrombin cleavage site is Phe/Gly-Pro-Arg (see for example Rezaie et al., U.S. Patent No. 5,298,599, column 6, lines 27-33), applicants have failed to sufficiently describe the claimed invention because of the lack of description on the tetrapeptide of LGPR or LGRP (claim 11) as the cleavage site recognized by thrombin.

In response, applicants respectfully traverse the Examiner's rejection. As discussed above, applicants maintain that the amendment of "GPR" to "LGPR" in the specification merely relates to an obvious error, and does not introduce new matter, at least for the following reasons. First, the examples in the present application only relate to the technical solution, which utilize the linker peptide "GSLGPR", but not "GSGPR". In example 3, the fusion protein STH (staphylokinase linked to hirudin via the sequence "GSLGPR" recognized by thrombin) is prepared. Accordingly, from example 3, one of ordinary skill in the art will recognize that "GSGPR" is obviously wrong. Furthermore, the inventors determined the nucleotide sequence for the fusion protein STH. A copy of the sequencing results, which shows that the nucleotide sequence for the linker peptide between staphylokinase and hirudin is "GGA TCC CTG GGT CCG CGT", which corresponds to the amino acid sequence "GSLGPR", is attached hereto as **Exhibit D**.

Additionally, it is known in the art that the peptide bond recognized and cleaved by thrombin is the one formed by the carboxyl group of lysine or arginine and the amino group of the downstream amino acid.

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 12

Accordingly, the recognition sequences for thrombin are not unique, and many short peptides comprising lysine or arginine may be recognized and cleaved by thrombin. See, e.g., Richard J. Jenny et al., Protein Expression and Purification, 2003, 31: 1-11 at page 2, right hand column paragraph 3, Table 1 and Table 2; see also, U.S. Patent No. 5,298,599, column 6, lines 27-33, which shows that the linker peptide "GSLGPR" may be recognized and cleaved by thrombin. Copies of Jenny et al. and U.S. Patent No. 5,298,599 are attached hereto as **Exhibit E** and **Exhibit F**, respectively.

Applicants also note that claim 11 has been amended to state that the tetrapeptide is LGPR, not LGRP.

Applicants submit that, in view of the preceding remarks, claims 8, 9 and 11 meet the requirements of 35 U.S.C. §112, First Paragraph for the reasons stated hereinabove. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection of claims 8, 9 and 11 under 35 U.S.C. §112, First Paragraph.

**Rejection under 35 U.S.C. §112, First Paragraph**

The Examiner rejected claims 1-8 and 11-15 under 35 U.S.C. §112, First Paragraph, as failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleged that the specification does not describe any venom or mutant of a thrombolytic protein or an anticoagulant protein. The Examiner also alleged that while the specification provides specific examples of fusion proteins of SAK-GSIEGR-HV2 and SAK-GSLGPR-HV2 (Examples 1 and 2), the specification does not provide sufficient description for a genus of variants of the fusion proteins comprising various thrombolytic proteins, anticoagulant proteins and linker peptides when there is substantial variation in the whole genus of fusion proteins.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution and without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 2 and 4 to remove reference to the use of "venom". Applicants have also amended claim 1 to recite that the linker peptide is recognized by blood coagulation factor. Applicants have amended claims 12 and 15 to depend from claim 1 and have canceled claims 6, 13 and 14.

Applicants note that claim 1 has been amended to recite that the linker peptide is, specifically, a peptide that is recognized by blood coagulation factor. Applicants also note that claim 11 recites linking a thrombolytic protein gene and an anticoagulant protein gene together via a sequence encoding IEGR or LGPR containing peptide so as to form a fusion protein. Applicants also note that the molecules listed in claim 2, i.e. staphylokinase (SAK), tissue-type plasminogen activator (t-PA), streptokinase (SK), urokinase (UK), and urokinase-like plasminogen activator (u-PA) all belong to the thrombolytic proteins while the molecules listed in claim 4, i.e. hirudin and antithrombin II, belong to the anticoagulant proteins. Mutants of these proteins are still proteinous molecules and can therefore still be linked to either an anticoagulant protein or a thrombolytic protein via the linker peptide of the present invention in order to form a fusion protein. Based on the common knowledge in the art and the disclosures contained in the present application, a person skilled in the art will appreciate that other thrombolytic proteins or anticoagulant proteins, in addition to those explicitly discussed in examples 1-3 of the present invention, can also be used to form a fusion protein via the linker peptide of the present invention, and achieve the purpose of the present invention. Applicants note that as long as a molecule is a protein, it can be linked to another protein via the linker peptide of the present invention in order to form a fusion protein - if the protein has thrombolytic activity, the resulting fusion protein will also have thrombolytic activity; if the protein has anticoagulant activity, the resulting fusion protein will also have thrombolytic activity. Accordingly, the present invention as stated in amended

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 14

claims 1, 2 and 4 and claim 11 would convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants submit that, in view of the preceding remarks, claims 1, 2, 4 and 11 meet the requirements of 35 U.S.C. §112, First Paragraph, and meet the written description requirement for the reasons stated hereinabove. Claims 3, 5, 7, 8, 12 and 15 depend from claim 1 and are submitted to meet the written description requirement for the same reasons. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-5, 7, 8, 11, 12 and 15 under 35 U.S.C. §112, First Paragraph.

**Rejection under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected claims 2, 4 and 13-14 under 35 U.S.C. §112, Second Paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that claims 2 and 4 are indefinite because of the use of the term "venom and mutants thereof." The Examiner alleged that the term cited renders the claim indefinite, as it is allegedly not clear what the term means with respect to the thrombolytic protein and the anticoagulant protein, and what structures the venom or mutants of the proteins have. The Examiner also alleged that since claims 13 and 14 do not set forth any steps involved in the claimed method/process, it is unclear what method/process applicant is intending to encompass.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution and without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 2 and 4 to remove reference to the use of "venom" and have canceled claims 13 and 14.

Applicants note that the term "mutants thereof" is clear as it refers to mutants of the proteins mentioned in claims 2 and 4, which will also have thrombolytic activity and anticoagulant activity, respectively.

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 15

Accordingly, applicants maintain that claims 2 and 4 as amended particularly point out and distinctly claim the subject matter which applicants regard as their invention. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection of claims 2 and 4 under 35 U.S.C. §112, Second Paragraph.

#### **Rejection Under 35 U.S.C. 102**

The Examiner rejected claims 1-7 and 11-14 under 35 U.S.C. §102(b), asserting that these claims are anticipated by van Zyl et al., (Thrombosis Research 88, 419-426 (1997)). The Examiner stated that van Zyl et al teach the production of recombinant antithrombotic and fibrinolytic protein, PLATSAK in *E. coli*, wherein the PLATSAK gene comprises staphylokinase, fused via a cleavable linker by FXa to an antithrombotic peptide of 29 amino acids comprising RGD sequence, a part of fibrinopeptide A and the tail of hirudin, wherein the purified protein has antithrombin activity, antiplatelet activity and fibrinolytic activity.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution and without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 1 and 11 to state that the fusion protein is cleavable and have canceled claims 6 and 13-14.

Applicants note that the present invention as recited in claim 1 as amended hereinabove provides a fusion protein, comprising a thrombolytic protein, an anticoagulant protein, and a cleavable linker peptide recognized by blood coagulation factor. Applicants also note that the present invention as recited in claim 11 provides a method for preparation of a fusion protein comprising a thrombolytic protein and an anticoagulant protein, wherein said method comprises linking the thrombolytic protein gene and the anticoagulant protein gene together via a sequence encoding IEGR or LGPR containing peptides so as to form the fusion protein gene, and then expressing said fusion protein gene in *E. coli*, yeast or animal cells to produce said fusion protein.



The fusion protein disclosed by van Zyle et al. is aimed to treatment for thrombosis with less hemorrhagic side effects. However, the fusion protein of van Zyl et al. significantly lengthened apTT and TT values which reveal the risk of hemorrhagic side effects, the reduction of which is one of the problems solved by the present invention (van Zyl et al., p. 423). Additionally, van Zyl et al do not state the mechanism of interaction of the fusion protein with thrombin and provide no data to show whether the antithrombin activity is due to the hirudin or the fibrinopeptide A components (van Zyl et al., p. 423).

In contrast to the fusion protein of van Zyl et al., the fusion protein of the present invention was selected after screening numerous fusion proteins for one that has no anticoagulant effects, i.e. no hemorrhagic side effects, before cleavage, which could be cleaved quickly into functional components to exert their therapeutic effects (i.e. within ten minutes as indicated by Experiment 1) and which showed effectiveness *in vivo*. In contrast, as stated above, the fusion protein of van Zyl et al. increases hemorrhagic side effects.

Moreover, to treat thrombosis with less hemorrhagic side effects, the fusion protein itself should be with less hemorrhagic effect and should be activated by cleavage by factor Xa or thrombin quickly into functional components to exert the therapeutic effect. However, many experiments have demonstrated that there are troubles associated with the use of thrombin or factor Xa to cleave fusion proteins. For instance, there is no evidence to prove that the linker site in any fusion proteins can be successfully cleaved by thrombin or factor Xa. See, e.g., Raftery, et al., *Protein Expr. Purif.* Vol. 15 (1999), pp. 228-235, a copy of which is attached hereto as Exhibit G; Muse, et al., *J. Bacteriol.*, Volume 181 (1999), pp. 934-940, a copy of which is attached hereto as Exhibit H; Belmouden, et al., *Eur. J. Biochem.*, Vol. 214 (1993), pp. 17-25, a copy of which is attached hereto as Exhibit I; Ko, et al., *J. Biol. Chem.*, Vol. 268 (1993), pp. 24330-24338, a copy of which is attached hereto as Exhibit J; Sharma, et al., *J. Biol. Chem.*, Vol. 270 (1995), pp. 14085-14093, a copy of which is attached hereeto as Exhibit K; and Wang, et al., *Biochem. J.*, Vol. 338 (1999) pp. 77-81,

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 17

a copy of which is attached hereto as Exhibit L. The efficiency of the cleavage by thrombin or factor Xa is quite different for different fusion proteins and is sometimes of no effect. See, e.g. Jenny et al., *Protein Expression and Purification*, Vol. 31 (2003), pp. 1-11, a copy of which is attached hereto as Exhibit E. Furthermore, Van Zyl et al. did not test the cleavage of the fusion protein PLATSAK by factor Xa and suggested that it was not cleaved (van Zyl et al., p.425, left column, lines 22-24). Accordingly, applicants maintain that van Zyl et al do not anticipate applicants' claimed invention as recited in amended claims 1 and 11.

Applicants note that claims 2-5, 7 and 12 depend from claim 1 and are also submitted to define patentable subject matter at least for the reasons set forth above.

The Examiner also rejected claims 1, 2, 4-7 and 11-15 under 35 U.S.C. §102(b), asserting that these claims are anticipated by Dawson et al., U.S. Patent 5,434,073 ("Dawson et al."). The Examiner stated that Dawson et al. teach the production of fusion proteins by linking together fibrinolytic and/or anti-thrombotic protein with a cleavable linker or thrombin cleavage site, their preparation, pharmaceutical compositions comprising the fusion proteins and their use in the treatment of thrombotic diseases.

In response, applicants note that the present invention as recited in claim 1 as amended hereinabove provides a fusion protein, comprising a thrombolytic protein, an anticoagulant protein, and a cleavable linker peptide recognized by blood coagulation factor. Applicants also note that the present invention as recited in claim 11 provides a method for preparation of a fusion protein comprising a thrombolytic protein and an anticoagulant protein, wherein said method comprises linking the thrombolytic protein gene and the anticoagulant protein gene together via a sequence encoding IEGR or LGPR containing peptides so as to form the fusion protein gene, and then expressing said fusion protein gene in *E. coli*, yeast or animal cells to produce said fusion protein.

The fusion protein disclosed by Dawson et al. is aimed to treatment for thrombosis with less hemorrhagic side effects. In contrast to the fusion protein of Dawson et al., the fusion protein of the present invention was selected after screening numerous fusion proteins for one that has no anticoagulant effects, i.e. no hemorrhagic side effects, before cleavage, which could be cleaved quickly into functional components to exert their therapeutic effects (i.e. within ten minutes as indicated by Experiment 1) and which showed effectiveness *in vivo*. In contrast, the fusion protein of Dawson et al. does not clearly indicate the time required for cleavage by factor Xa of a Hirudin-IEGR-Hirudin fusion protein (see Ex. 3) and indicates that the time required for cleavage of a streptokinase-streptokinase fusion gene by thrombin was fourteen hours, which is far too long to be able to exert thrombolytic effect as a therapeutic drug. Additionally, data for cleavage of streptokinase-IEGR-hirudin (example 14) and Hirudin-IEGR-streptokinase (Ex. 15) were not listed, and therefore do not indicate that the cleavage effect was positive for this particular fusion protein construct. Moreover, Dawson et al. do not indicate the behavior of the fusion protein in an *in vivo* experiment.

To treat thrombosis with less hemorrhagic side effects, the fusion protein itself should be with less hemorrhagic effect and should be activated by cleavage by factor Xa or thrombin quickly into functional components to exert the therapeutic effect. However, many experiments have demonstrated that there are troubles associated with the use of thrombin or factor Xa to cleave fusion proteins. For instance, there is no evidence to prove that the linker site in any fusion proteins can be successfully cleaved by thrombin or factor Xa. See, e.g., Raftery, et al., *Protein Expr. Purif.* Vol. 15 (1999), pp. 228-235, a copy of which is attached hereto as Exhibit G; Muse, et al., *J. Bacteriol.*, Volume 181 (1999), pp. 934-940, a copy of which is attached hereto as Exhibit H; Belmouden, et al., *Eur. J. Biochem.*, Vol. 214 (1993), pp. 17-25, a copy of which is attached hereto as Exhibit I; Ko, et al., *J. Biol. Chem.*, Vol. 268 (1993), pp. 24330-24338, a copy of which is attached hereto as Exhibit J; Sharma, et al., *J. Biol. Chem.*, Vol. 270

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 19

(1995), pp. 14085-14093, a copy of which is attached hereto as Exhibit K; and Wang, et al., *Biochem. J.*, Vol. 338 (1999) pp. 77-81, a copy of which is attached hereto as Exhibit L. The efficiency of the cleavage by thrombin or factor Xa is quite different for different fusion proteins and is sometimes of no effect. See, e.g. Jenny et al., *Protein Expression and Purification*, Vol. 31 (2003), pp. 1-11, a copy of which is attached hereto as Exhibit E. As stated above, Dawson et al. did not test the cleavage of a Streptokinase-IEGR-Hirudin or a Hirudin-IEGR-Streptokinase fusion protein by factor Xa or by thrombin, and suggested that the fusion protein that was cleaved by thrombin took fourteen hours to cleave, which would prevent it from working as a therapeutic drug (Dawson et al., Ex. 3, 13-15). Accordingly, applicants maintain that Dawson et al do not anticipate applicants' claimed invention as recited in amended claims 1 and 11.

Applicants note that claims 2, 4-5, 7, 12 and 15 depend from claim 1 and are also submitted to define patentable subject matter at least for the reasons set forth above.

The Examiner also rejected claims 12 and 15 under 35 U.S.C. §102(b), asserting that these claims are anticipated by Potter et al., U.S. Patent 6,015,787 ("Potter et al."). The Examiner stated that Potter et al. teach the use of a fusion protein comprising a calpastatin peptide and a signal peptide capable of delivering the fusion protein into a cell, where the fusion protein can be prepared as a therapeutic composition and can be used in reduction of coronary thrombosis in coronary bypass surgery, reduction of thrombosis and other thrombosis associated diseases. The Examiner noted that since the claims do not recite the structure of the fusion protein, any fusion protein that is in a pharmaceutical composition or that treats thrombosis would meet the criteria of the claims.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution and without conceding the correctness of the Examiner's position, applicants have hereinabove

Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 20

amended claims 12 and 15 to state that the fusion protein is the fusion protein according to claim 1. Accordingly, applicants maintain that Potter et al do not anticipate applicants' claimed invention as recited in amended claims 12 and 15.

#### **Claim Objections**

The Examiner objected to claim 10 as being dependent upon a rejected base claim, but stated that it would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

In response, applicants have rewritten claim 10 in independent form including all of the limitations of the claim on which it previously depended. Accordingly, applicants maintain that claim 10 is allowable.

#### **Summary**

In view of the remarks hereinabove, applicants respectfully submit that the grounds of rejection set forth in the May 11, 2009 Office Action have been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw these grounds of rejection and indicate that the claims are allowable.

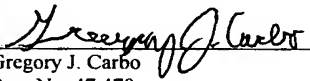
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fees, other than the enclosed \$1,110.00 three-month extension fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

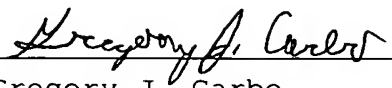
Applicants: Bingxing Shi et al.  
U.S. Serial No.: 10/526,682  
Filed: March 2, 2005  
Page 21

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 November 12, 2009  
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